

REMARKS/ARGUMENTS

Claims 1, 13, 14, 15 and 35 have been amended to recite an aqueous suspension comprising suspended solid steroidal anti-inflammatory particles having a specific particle size distribution profile. Support for these amendments is found at least on paragraph [0068] of the published patent application (i.e. U.S. Publication No. 2004/0209852). Claim 3 has been amended by removing the redundant period at the end of the claim. Claim 26 has been cancelled. Claims 27 and 28 have been amended to depend upon claim 1. Claim 30 has been amended to correct grammatical errors. Claim 13 has been amended to recite the following fluticasone particle size distribution profile: about 10% or less of the steroidal anti-inflammatory particles have a particle size of less than 0.40 microns; about 25% or less of the steroidal anti-inflammatory particles have a particle size of less than 0.75 microns; about 50% or less of the steroidal anti-inflammatory particles have a particle size of less than 1.50 microns; about 75% or less of the steroidal anti-inflammatory particles have a particle size of less than 3.0 microns; and about 90% or less of the steroidal anti-inflammatory particles have a particle size of less than 5.2 microns. Since the present application is a continuation-in-part of Ser. No. 10/414,682 and Ser. No. 10/414,756, and has incorporated both applications by reference in their entirety, pursuant to 37 CFR 1.57, proper support for this amendment is found at least on paragraphs [0088] – [0089] (including Tables 1 and 2).

New claims 71-72 are dependent upon independent claim 1 and recite a complexing agent. New claims 73-74 are dependent upon independent claim 35 and recite a complexing agent. Support for all of the new claims is found at least on paragraph [0063] of the published application (i.e. U.S. Publication No. 2004/0209852).

Claims 1, 3-6, 10-15, 22-30, 35 and 71-74 are pending.

Claim Objections

Claims 3 and 30 stand objected to by the Office. Specifically, the Office has objected to claim 3 for including two periods at the end of the claim. Accordingly, claim 3 has been amended by deleting the redundant period. Claim 30 stands objected for reciting chemical compounds being capitalized. Claim 30 has been amended such that the chemical compounds are no longer capitalized.

Specification

The specification has been objected to for using not capitalizing the trademark "THE PHYSICIAN'S DESK REFERENCE®." Paragraph [0041] has been amended accordingly.

Rejections under 35 U.S.C. §112

Claims 1, 3-6, 10-15, 26-28 and 30 stand rejected under 35 U.S.C. §112, second paragraph, as being indefinite. The Office argues that "a pharmaceutically acceptable derivative of fluticasone" as recited in the claims is unclear because the application does not specifically define what is meant by the term "derivative". Further, the Office contends that carbon dioxide could theoretically be derived from the combustion of fluticasone as support for concluding that the skilled artisan would not be apprised of the metes and bounds of the term "derivative."

However, applicant notes that paragraph [0032] of U.S. Publication 2004/0209852 defines the term "derivative" as including "any salt, ester, enol ether, enol ester, acid, base, solvate or hydrate thereof." As such, the skilled artisan would readily recognize the "metes and bounds" of this term in light of both the skill in the art and the teaching provided in the application. Applicant requests withdrawal of this rejection.

Claim 26 stands rejected under 35 U.S.C. §112, second paragraph, as being indefinite because for "particulate fluticasone that is dissolved (i.e. in an aqueous solution) to have the particle size distribution of parent claim 1." Claim 26 has been cancelled.

Rejections under 35 U.S.C. §103

Claims 1, 3-6, 10-15, 22-26 and 28-30 stand rejected under 35 U.S.C. §103(a) as being obvious over U.S. Publication No. 2002/0061281 to Osbakken et al. (hereinafter "Osbakken") in view of U.S. Patent No. 5,958,378 to Waldrep et al. (hereinafter "Waldrep"), WO 02/00199 to Lancaster et al. (hereinafter "Lancaster"), and WO 01/32125 to Ferrie et al. (hereinafter "Ferrie"). Claims 27 and 35 under 35 U.S.C. §103(a) as being obvious over Osbakken in view of Waldrep, Lancaster, and Ferrie, and further in view of U.S. Patent No 6,464,958 to Bernini et al. (hereinafter "Bernini"). **Applicant respectfully traverses these rejections.**

Primary Reference: Osbakken

In general, Osbakken is directed to pharmaceutical compositions including one or more active ingredients. Specifically, Osbakken is directed to compositions having a specific surface

tension to yield a liquid aerosol cloud for inhalation having a mass median aerodynamic diameter (MMAD) of between 0.5 and 10 microns. Osbakken teaches adjusting the surface tension of a solution such that it yields a liquid aerosol cloud having an MMAD in a pre-determined range. For example, Osbakken teaches that “this aerosol cloud will have liquid aerosol particles” having certain MMAD ranges. Further, Osbakken stresses the importance of controlling the surface tension of the composition so that the liquid droplets are deposited in the appropriate locations of a patient. See paragraph [0092].

To illustrate the compositions contemplated, Osbakken provides a detailed description of how the compositions are prepared so that they can form liquid aerosol particles of a given diameter. See paragraph [0103] through [0116]. Particularly, Osbakken teaches that the medicaments are mixed with diluent and “filtered with a coarse filter and then a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron)”. See paragraph [0104]. Furthermore, Osbakken teaches that unit doses will “be dissolved in a solvent such as water or saline solution...” in a specified volume. See paragraph [0104]. As such, the compositions taught by Osbakken cannot include suspended solid drug substances because the preparation step of filtering through “a fine filter (5 micron, 2 micron, 1 micron, 0.45 micron, or 0.22 micron)” would result in the undesirable removal of the drug substances from the composition.

Additionally, Osbakken teaches that “Laser diffraction is the most accurate way for measuring wet aerosols (droplets of liquids).” See paragraph [0114]. Therefore, Osbakken provides that “the preferred method for measuring the size of particles [liquid droplets] in aerosols as contemplated by the present invention is by laser diffraction.” See paragraph [0114]. The fact that Osbakken points out that laser diffraction is the most accurate “way for measuring wet aerosols (droplets of liquids)” and therefore uses this method is further evidence that the MMAD ranges discussed by Osbakken are directed to liquid droplets, not suspended solid particulates of drug substances in an aqueous medium.

Further, the term “dissolution” as set forth in *Hawley's Condensed Chemical Dictionary*, 14th Edition, is defined as “molecular dispersion of a solid in a liquid.” Therefore, the Osbakken compositions contain the drug substances in a dissolved state wherein the drug substances are molecularly dispersed in a liquid such that they lose their crystalline (solid) form. Therefore, it is

clear from the terminology (i.e. dissolved in a solvent such as water or saline solution) and teachings of Osbakken that the contemplated compositions do not contain solid particulates of drug substances suspended in an aqueous medium.

For instance, 12 of the 13 examples provided in Osbakken include filtering the composition through a 0.22 micron filter. As noted above, if the compositions contemplated by Osbakken included suspended solids of drug substances, they would be undesirably removed due to the filtration. Applicant notes that the outstanding example, namely example 12, teaches dissolving the powders. See paragraph [0203]. Accordingly every example provided by Osbakken to illustrate the contemplated compositions includes the molecular dispersion of the solid drug substances such that they lose their crystalline form.

Therefore, despite Osbakken stating that the compositions can be formulated as a solution or suspension, Osbakken does not provide a single teaching regarding a composition including suspended solid drug particulates. Consequently, it is clear from reading Osbakken as a whole that the compositions contemplated, and thus extensively taught, include the dissolution of drug substances and not the suspension of drug particulates in an aqueous medium.

As such, Osbakken does not teach any solid particle size distribution for any active agent. The current claims recite specific particle sizes distributions for suspended solid fluticasone particles, not liquid droplets. Since Osbakken is silent regarding any such suspended solid fluticasone particle size distribution, Osbakken does not teach or suggest particle size distributions of fluticasone, much less the currently claimed distributions.

Secondary References: Waldrep, Lancaster, Ferrie and Bernini

The Office cites Waldrep, for support that MMAD (as mentioned in Osbakken) is recognized as representing "the central point in a distribution of particle sizes." Waldrep is directed to high dose liposome compositions of cyclosporine A or Budesonide. More specifically, Waldrep teaches a high dose cyclosporine A-liposome composition having up to about 30 mg/ml cyclosporine A in up to about 225 mg of a phospholipid/ml starting reservoir concentration and a high dose budesonide-liposome composition having up to 15mg/ml budesonide in up to about 225 mg of a phospholipid/ml starting material. The current claims are not directed to liposome formulations, let alone high dose liposome compositions.

The Office cites Lancaster for demonstrating that art recognized methods of preparing pharmaceutical particulate particles yields a composition comprising a distribution of particle sizes. Lancaster is directed to a process for preparing crystalline particles by mixing a flowing solution of a desired drug substance with a flowing liquid anti-solvent to precipitate the desired substance. The mixing of the two flowing streams can be carried out in a cylindrical mixing chamber such that the two streams are intimately mixed by formation of a vortex and causing precipitation. The current claims are not directed to a process for precipitating particles.

Similar to Lancaster, the Office cites Ferrie for demonstrating that particulate medicament compositions made by methods known in the art are comprised of distributions of particle sizes. Ferrie is directed to an apparatus and process for preparing crystalline particles of drug substances. The apparatus includes (i) a first reservoir having a drug substance dissolved in a liquid solvent; (ii) a second reservoir of liquid antisolvent which is miscible with the liquid solvent in the first reservoir; (iii) a cylindrical mixing chamber having first and second tangential inlet ports and an axial outlet port; (iv) means for delivering the contents of the first and second reservoirs to the mixing chamber in a stream via the first and second inlet ports respectively at independent controlled flow rate such that the streams are intimately mixed in the cylindrical mixing chamber through formation of a vortex thereby causing precipitation of the drug substance; and (vi) means for collecting the discharged precipitated particles such as by filtering. The current claims are not directed to an apparatus or process for precipitating particles.

The Office acknowledges that Osbakken, Waldrep, Lancaster and Ferrie lack the teaching of compositions in a metered-dose pump spray. The Office cites Bernini for curing this deficiency. Bernini is directed to a process for preparing aqueous suspensions for inhalation. Bernini's process includes the following steps: (i) preparing an aqueous solution constituting the carrier and optionally containing wetting agents, surfactants, viscosity-increasing agents, stabilizing agents, isotonicity agents and/or buffers, in a suitable turboemulsifier vessel; (ii) sterilizing the aqueous base inside the same container; (iii) adding, in a sterile environment, one or more active sterile micronised ingredients; and (iv) dispersing all of the ingredients by using the same turboemulsifier. The resulting compositions are intended for nebulization.

The Office relies on Waldrep, Lancaster and Ferrie for support that the MMAD teachings provided in Osbakken are recognized by the skilled artisan to disclose the central point in a distribution of particle sizes. However, Osbakken's MMAD droplet teachings are not cured by Waldrep, Lancaster and/or Ferrie. Despite Waldrep's teachings of MMAD being a central point of some distribution and Lancaster and Ferrie's teachings that precipitation processes result in distributions of particle sizes, none of these references cure the deficiency of Osbakken's liquid droplet teachings. Further, Osbakken, alone or in any combination with Waldrep, Lancaster, Ferrie or Bernini, does not disclose each and every limitation of independent Claims 1 and 35; namely an aqueous suspension of fluticasone having the specifically recited solid particle size distributions in an aqueous medium suitable for administration to the nasal-paranasal mucosa. Additionally, any combination of the cited references also does not teach or suggest 7.5 to 15 mg of amphotericin β , much less in combination with the specifically recited solid fluticasone particle size distribution as recited in independent claim 35. Therefore, Applicant respectfully requests withdrawal of the obviousness rejections.

Cited References Do Not Teach or Suggest All Claimed Elements

The cited references have been discussed in detail above.

The Office has not proven a *prima facie* case of obviousness because none of the cited references cited teach or suggest any of the following: (1) a formulation comprising an aqueous suspension including the claimed particle size distribution of fluticasone suitable for administration to the nasal-paranasal mucosa; (2) a formulation including a complexing agent and (3) the combination of the claimed particle size distribution of fluticasone and a complexing agent. Since Osbakken, Waldrep, Lancaster, Ferrie and Bernini all fail to teach or suggest these elements, any combination of these references also fails to teach or suggest these claimed elements. For instance, all references are silent regarding a complexing agent. Therefore, any combination of the cited references will also lack a complexing agent.

As discussed above, any combination of the cited references does not teach or suggest an aqueous suspension of fluticasone particles having the claimed particle size distribution. Also noted above, Osbakken does not provide any teaching regarding a composition including suspended solid drug particulates, let alone fluticasone particles having the claimed distribution

profile. Compositions according to Osbakken's teachings and examples include a drug substances and not the suspension of drug particulates in an aqueous medium. Again, the secondary references do not cure Osbakken's failure to teach an aqueous suspension of fluticasone particles having the recited distribution profile.

Not one of the cited references teaches or suggests a complexing agent. As such, none of the cited references teach or suggest the combination of the claimed fluticasone particle size distribution and a complexing agent as recited in the dependent claims 71-74. Furthermore, not one of the cited references teaches or suggests a formulation suitable for administration to the nasal-paranasal mucosa including any of the following complexing agents: sodium edetate (claims 71- 74); ethylenediaminetetraacetic acid (claims 71 and 73), citric acid (claims 71 and 73) or nitrilotriacetic acid (claims 71 and 73).

All of the cited references, alone or in any combination simply do not teach or suggest a formulation including a complexing agent. Moreover, not one of the references discusses the desirability of including a complexing agent in a formulation suitable for administration to the nasal-paranasal mucosa; much less the specific agents recited in the claims. Accordingly, any combination of the cited references also does not teach or suggest a nasal formulation including a complexing agent.

Since all of the cited references do not teach or suggest the following: (1) a formulation comprising an aqueous suspension including the claimed particle size distribution of fluticasone suitable for administration to the nasal-paranasal mucosa; (2) a formulation including a complexing agent and (3) the combination of the claimed particle size distribution of fluticasone and a complexing agent, any combination of Osbakken, Waldrep, Lancaster, Ferrie and Bernini also fails to teach or suggest these elements of the currently amended claims. Applicant submits that the obviousness rejection has been overcome and requests withdrawal of this rejection.

As such, the Office has not established a *prima facie* case of obviousness. Accordingly, Applicant requests the withdrawal of the obviousness rejections.

Unexpected Results

The present application is a continuation-in-part of Ser. No. 10/414,682 and Ser. No. 10/414,756, both of which were incorporated by reference in their entirety. See paragraph [0001] of the present application.

Pursuant to 37 CFR 1.57(d), "other material ("Nonessential material") may be incorporated by reference to U.S. patents, U.S. patent application publications, foreign patents, foreign published applications, prior and concurrently filed commonly owned U.S. applications, or non-patent publications." Further, 37 CFR 1.57(c) provides that "essential material" may be incorporated by reference, but only by way of an incorporation by reference to a U.S. patent or U.S. patent application publication, which patent or patent application publication does not itself incorporate such essential material by reference." Consequently, the present application's incorporation by reference of both parent applications in their entirety provides support for arguments based on any subject matter disclosed in either parent application. Accordingly, arguments based on subject matter or data provided in the parent applications is not new matter.

Applicant directs the Office's attention to commonly owned and copending U.S. Publication No. 2004/0208830 (Ser. No. 10/414,682), which was explicitly incorporated by reference in its entirety. Paragraphs [0053] – [0090] of the '830 application describe a study assessing the efficacy of Dey® fluticasone nasal sprays and its comparability with Flonase®. The results of which are exemplified on Figures 1-4 of the '830 application.

The study durations was 3 weeks and consisted of 2 phases. The first phase included 1 week baseline screening and the second phase included 2 weeks of treatment. Each patient was given a Total Nasal Symptom Score (TNSS) diary for recording daily TNSS. The daily TNSS was the sum of the signs and symptoms of rhinitis such as runny nose, nasal congestion, itch nose etc. After completing the baseline phase, the patients were split into 1 of 6 treatment groups: Dey-FP High Dose; Dey-FP Low Dose; Flonase® High Dose; Flonase® Low Dose; Placebo High Dose and Placebo Low Dose. At the end of weeks 2 and 3, assessments regarding the reflective and instantaneous TNSS results were made.

Although the instantaneous or "treatment-by-day" relief of signs and symptoms of rhinitis were somewhat similar for Dey-FP and Flonase groups, the magnitude of improvement in TNSS for the Dey-FP groups was higher than those of the Flonase groups. This unexpected

increase in the reduction of TNSS exhibited by the Dey-FP groups, as illustrated on Figure 1 or the '830 publication for example, over the 14 day treatment period provided a substantial improvement over existing fluticasone formulations. Particularly, Figure 1 not only shows that at the end of the 14 day treatment period that the Dey-FP Low Dose groups exhibited significantly better TNSS reduction than the Flonase[®] Low Dose Groups, but surprisingly that the Dey-FP Low Dose groups actually outperformed the Flonase[®] High Dose groups. Accordingly, the currently claimed formulations can provide patients with an increased reduction in the signs and symptoms of rhinitis than prior art formulations while administering less active (i.e. fluticasone). Consequently, patients can use less active and realize increased relief from rhinitis symptoms. Since the skilled artisan would only expect to achieve an improved reduction in the signs and symptoms of rhinitis by providing increased levels of active, these results are clearly unexpected by one skilled in the art. Accordingly, Applicant submits that the criticality of the currently claimed distributions is exemplified by these surprising results.

Applicant notes that Tables 1 and 2, found on paragraphs [0088]-[0089] of the '830 publication recite specific particle size distributions for fluticasone. These distributions have been explicitly captured in currently amended claim 13.

Double Patenting

The Office has asserted several provisional rejections based on the judicially created doctrine of non-statutory obviousness-type double patenting as follows:

- (i) Claims 1, 10-15 and 22-28 are provisionally rejected over claims 1, 3-6, 9-20 and 23 of copending Application No. 11/078,263;
- (ii) Claims 1, 10-13 and 22-28 are provisionally rejected over claims 1, 4, 6-10, 11-14 and 19 of copending Application No. 11/250,256 in view of Bernini; and
- (iii) Claims 1, 3-6 and 10-15 are provisionally rejected over claims 1-4, 7-8, 14-19 and 17-30 of copending Application No. 11/250,925 in view of Bernini.

In response to the provisional rejections, a terminal disclaimer is filed herewith to disclaim the terminal part of any statutory term for any patent granted on the pending application which would extend beyond the expiration date of the term of copending U.S. Application Nos. 11/078,263, 11/250,256 and 11/250,925 that may issue prior to the present application.

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Amendment Dated September 24, 2007
Reply to Office Action of April 23, 2007

Applicant submits that the terminal disclaimer overcomes the provisional rejection and puts the claims in condition for allowance.

Conclusion

In view of the amendments and remarks made above, Applicant submits that the pending claims are now in condition for allowance. Applicant respectfully requests that the claims be allowed to issue. If the Examiner wishes to discuss the application or the comments herein, the Examiner is urged to contact the undersigned by telephone.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those that may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

A handwritten signature in dark ink, appearing to read "John E. Johnson, III", with a stylized flourish at the end.

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disodium orthophosphate. See sodium phosphate, dibasic.

disodiumphenyl phosphate. $C_6H_5Na_2PO_4$.
Properties: White powder. Soluble in water; insoluble in acetone and ether.
Use: Reagent for milk pasteurization.

disodium phosphate. See sodium phosphate, dibasic.

disodium pyrophosphate. See sodium pyrophosphate, acid.

disodium tartrate. See sodium tartrate.

disperse dye. See dye, disperse.

disperse phase. See phase (2); colloid chemistry.

dispersing agent. A surface-active agent added to a suspending medium to promote uniform and maximum separation of extremely fine solid particles, often of colloidal size. True dispersing agents are polymeric electrolytes (condensed sodium silicates, polyphosphates, lignin derivatives); in non-aqueous media sterols, lecithin and fatty acids are effective.

Use: Wet-grinding of pigments and sulfur; preparation of ceramic glazes, oil-well drilling muds, insecticidal mixtures, carbon black in rubber, and water-insoluble dyes.

See emulsion; detergent.

dispersion. (1) A two-phase system where one phase consists of finely divided particles (often in the colloidal size range) distributed throughout a bulk substance, the particles being the disperse or internal phase, and the bulk substance the continuous or external phase. Under natural conditions, the distribution is seldom uniform; but under controlled conditions, the uniformity can be increased by addition of wetting or dispersing agents (surfactants) such as a fatty acid. The various possible systems are: gas-liquid (foam), solid-gas (aerosol), gas-solid (foamed plastic), liquid-gas (fog), liquid-liquid (emulsions), solid-liquid (paint), and solid-solid (carbon black in rubber). Some types, such as milk and rubber latex, are stabilized by a protective colloid that prevents agglomeration of the dispersed particles by an adherent coating. Solid-in-liquid colloidal dispersions (loosely called solutions) can be precipitated by adding electrolytes that neutralize the electrical charges on the particles. Larger particles will gradually coalesce and either rise to the top or settle out, depending upon their specific gravity. See suspension; colloid chemistry. (2) In the field of optics, dispersion denotes the retardation of a light ray, usually resulting in a change of direction as it passes into or out of a substance, to an extent depending on the frequency. Dispersion is a critically

important property of optical glass.
 See refraction.

"Dispersite" [Uniroyal]. TM for water dispersions of natural, synthetic, and reclaimed rubbers and resins.

Use: Adhesives for textiles, paper, shoes, leather, tapes; coatings for metal, paper, fabrics, carpets; protective (strippable) for saturating paper, felt, book covers, tape, jute pads; for dipping tire cords. Can be applied by spraying, spreading, impregnation, saturation.

"Disperson" [Crompton & Knowles]. TM for wettable grades of zinc, calcium, and other metallic stearates.

Use: Where easy dispersion in water is desired.

"Disperson OS" [ICI]. TM for an oil-soluble emulsifying agent composed of an 8% solution of a polyethenoxy compound in isopropanol. Designed especially for dispersion of oil spills in seawater. Claimed to be biodegradable and to have low toxicity for fish and other marine organisms. Amount needed said to be from 20 to 25% of the oil volume.

displacement. Chemical change in which one element enters a compound in place of another, the latter being set free.

displacement series. See activity series.

disposal, waste. See waste control; chemical waste; radioactive waste.

disproportionation. A chemical reaction in which a single compound serves as both oxidizing and reducing agent and is thereby converted into a more oxidized and a more reduced derivative. Thus, a hypochlorite upon appropriate heating yields a chlorate and a chloride, and an ethyl radical formed as an intermediate is converted into ethane and ethylene.

See transalkylation.

dissociation. The process by which a chemical combination breaks up into simpler constituents as a result of either (1) added energy, as in the case of gaseous molecules dissociated by heat, or (2) the effect of a solvent on a dissolved polar compound (electrolytic dissociation), e.g., water on hydrogen chloride. It may occur in the gaseous, solid, or liquid state, or in solution. All electrolytes dissociate to a greater or less extent in polar solvents. The degree of dissociation can be used to determine the equilibrium constant for dissociation, an important factor in ascertaining the extent of a chemical process. See ionization.

dissolution. Molecular dispersion of a solid in a liquid.